PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

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Applicant's or agent's file reference P770PC00	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/DK2004/000527	International filing date *(day/month/year)* 06.08.2004	Priority date *(day/month/year)* 07.08.2003

International Patent Classification (IPC) or national classification and IPC
C07K19/00, C07K14/705, C07K14/78, C07K14/52, C12N9/64, A61K38/17, A61K38/43, A61K38/19, A61K38/39

Applicant
ENKAM PHARMACEUTICALS A/S et al.

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 12 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 13 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☒ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☒	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
06.09.2005	04.11.2005

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/DK2004/000527

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-101 as originally filed

   Claims, Numbers

   1-34 received on 08.09.2005 with letter of 06.09.2005

   Drawings, Sheets

   1/28-28/28 as originally filed

   ☒ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☒ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☒ the claims, Nos. 11 with respect to the definition of the term "homologue"
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-34 (all partially), and 34 also as to IA

because:

☒ the said international application, or the said claims Nos. 34 as to IA relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 11-34 (all partially) are so unclear that no meaningful opinion could be formed *(specify)*:

see separate sheet

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 1-34 (all partially)

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. IV Lack of unity of invention

1. ☐ In response to the invitation to restrict or pay additional fees, the applicant has:
   - ☐ restricted the claims.
   - ☐ paid additional fees.
   - ☐ paid additional fees under protest.
   - ☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 12,14,17-19 (completely) and 1-11,13,15,16,20-34 (partially) .

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-34
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-34
Industrial applicability (IA)	Yes:	Claims	1-33
	No:	Claims	

2. Citations and explanations (Rule 70.7):

   see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

   and / or

2. Non-written disclosures (Rule 70.9)

   see separate sheet

Supplemental Box relating to Sequence Listing

Continuation of Box I, item 2:

1. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this report has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed

   ☐ filed together with the international application in computer readable form

   ☒ furnished subsequently to this Authority for the purposes of search and/or examination

   ☒ received by this Authority as an amendment on

2. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional observations, if necessary:

Re Item I

Basis of the report

According to the description on page 33, lines 24-26, a "homologue in the present context is defined as an amino acid sequence which has less than 60% and more than 19% [...] homology to any of the sequences set forth in SEQ ID NOs: 1-146". However, the limitation of less than 60% homology is missing in amended claim 11, leading to an extension beyond the content of the application as filed, contrary to Article 34.2(b) PCT and Rule 70.2(c) PCT.

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Present claims 1-10 and 20-34 relate to an extremely large number of possible compounds.
Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope was impossible.
It is unclear in the sense of Article 6 PCT what is meant with a sequence of formula L1-A-L2-B-L3-C-L4-D-L5 as defined in claim 1. This expression comprises a wide range of compounds and is therefore speculative, embracing a great variety of possibilities not yet explored by the applicant, the effect of which cannot be expected by the skilled person using the teaching disclosed in the current application and his technical knowledge to reproduce without undue burden all the possibilities which are actually claimed, contrary to Article 5 PCT.

Moreover, the scope of claims 11-34, in as far as the expressions "(functional) homologues", "fragments", or "variants" (see e.g. claim 12) are concerned, is so unclear (Article 6 PCT) that a meaningful international search is impossible with regard to these expressions.

In addition, the amended portions in claim 11 wherein the term fragment is defined by having at least 40% of the length of a sequence of SEQ ID NOs 1-146 and wherein the term variant is defined as having at least 60% homology to a sequence of SEQ ID NOs 1-146 have not been searched and are therefore not examined (Rule 66.1(e) PCT).

The search has been carried out for those parts of the claims which appear to be supported and disclosed, and which belong to the first and second inventions, namely those parts relating to the compounds, wherein at least one of the two peptide sequences is a peptide fragment having the amino acid sequence of SEQ ID NOs: 1 and/or 2. Consequently, the examination is being carried out for those parts of the claims which appear to be supported and disclosed, and which belong to the first invention, namely those parts relating to the compounds, wherein at least one of the two peptide sequences is a peptide fragment having the amino acid sequence of SEQ ID NOs: 1 and/or 2 (Rule 66.1(e) PCT).

No international search was performed for subject-matter of claims 1-11,13-16,18 and 20-34 (all partially) due to an objection against unity of invention (see reasoning below).

Claim 34 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of claim 34 (Article 34(4)(a)(I) PCT).

Re Item IV
Lack of unity of invention

This Authority considers that there are 146 inventions covered by the claims indicated as follows:

1: Claims 12,17,19 (completely) and 1-11,13,15,16,20-34 (partially) directed to a compound wherein at least one of the two peptide sequences is a peptide fragment having SEQ ID NO: 1, and its use and method

2: Claims 14,18 (completely) and 1-11,13,15,16,20-34 (partially) directed to a

compound wherein at least one of the two peptide sequences is a peptide fragment having SEQ ID NO: 2, and its use and method

3-146: Claims 1-11,13,15,16,20-34 (all partially) directed to a compound wherein at least one of the two peptide sequences is a peptide fragment having SEQ ID NOs: 3-145, or 146, and its use and method

The reasons for which the inventions are not so linked as to form a single general inventive concept, as required by Rule 13.1 PCT, are as follows:

The problem to be solved by the present application resides in the provision of compounds for treatment or prevention of diseases that are associated with an FGFR, including stroke, Alzheimer's Disease, manic depression and diabetes mellitus type I and II.
Rule 13.2 PCT governs the situation involving a single claim that defines alternatives of chemical compounds, the so-called "Markush practice".
Unity of invention can only be acknowledged if the claimed compounds have a common property or activity and share a significant structural element. While a common property has been acknowledged, a significant structural element is not shared by the fusion proteins of the different inventions.
For example, fusion proteins comprising SEQ ID NO:1, EVYVVAENQQGKSKA, a fragment of NCAM FnIII,2, do not share a significant amino acid sequence with fusion proteins having SEQ ID NO:2, NIEVWVEAENALGKKV, a fragment of Interleukin-6 receptor beta chain.
The amino acid sequence of formula L1-A-L2-B-L3-C-L4-D-L5 and the linker X[(A)nCOOH][(B)mCOOH] are not considered as common structural element that may fulfil the role of a special technical feature in the sense of Rule 13.2 PCT, since a concrete partial amino acid sequence that is present in all fusion proteins is missing.

Furthermore, since (1) the linker molecule X[(A)nCOOH][(B)mCOOH] which is already known from WO 00/18791 does not impart the common property, and (2) fusion proteins that are capable of binding to FGFR and comprising SEQ ID NO: 1 of the present application are known from the international patent application WO 03/016351 (see pages 13-22,25; claims 1,17, 22), unity of invention cannot be acknowledged.

Finally, the single general inventive concept of the present application, based on the broad consensus sequence of claim 1 in connection with the linker sequence, lacks an inventive step over the cited prior art (see below under Item V). Thus, the single general common concept as defined above lacks inventive step (although novel) according to Rule 13.1 PCT.
As a consequence, the 146 different peptides claimed are no longer linked together and such a link can also not to be established by a common linker sequence which is not considered as a special technical feature.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: WO 03/016351 A (ENKAM PHARMACEUTICALS A/S; KISELYOV, VLADISLAV, V; SKLADCHIKOVA, GALIN) 27 February 2003 (2003-02-27)
D2: WO 01/16166 A (THE UNITED STATES OF AMERICA, REPRESENTED BY THE SECRETARY, DEPARTMENT) 8 March 2001 (2001-03-08)
D3: WO 00/18791 A (STATENS SERUM INSTITUT; HOLM, ARNE; JOERGENSEN, RIKKE, MALENE; OESTERG) 6 April 2000 (2000-04-06)

Novelty

The present application meets the criteria of Article 33(1) PCT, because the subject-matter of claims 1 to 34 is new in the sense of Article 33(2) PCT with view to the documents cited in the international search report.

Inventive step

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 1 does not involve an inventive step in the sense of Article 33(3) PCT.

The document D1 is regarded as being the closest prior art to the subject-matter of claim 1, in so far as it relates to SEQ ID NO:1, and discloses inter alia dimers comprising SEQ ID NO: 1 of the present application that are capable of binding to a fibroblast growth factor receptor (FGFR, see pages 13-23,25 and claims).

The document D2 is regarded as being the closest prior art to the subject-matter of claim 1, in so far as it relates to SEQ ID NO:2, and discloses inter alia fusion proteins comprising SEQ ID NO: 2 of the present application which are useful in the treatment of a variety of diseases, including diabetes (see pages 2,13 and 51 (peptide E20)). The document D2 does not explicitly mention the capability of the fusion protein to bind to FGFR, but discloses the treatment of at least some diseases that are also disclosed in the present application.

Subject-matter of claims 1 differs in that the peptide sequences are connected to each other through a linker of the general formula X[(A)nCOOH][(B)mCOOH].

The problem to be solved by the present application resides in the provision of further compounds for treatment or prevention of diseases that are associated with an FGFR, including stroke, Alzheimer's Disease, manic depression and diabetes mellitus type I and II.

The solution proposed in claim 1 of the present application cannot be considered as involving an inventive step (Article 33(3) PCT), since linkers of the formula X[(A)nCOOH][(B)mCOOH] for connecting different peptide sequences are known from the document D3 (see pages 15 and 34-36) for use in pharmaceutical preparations (see pages 15, 34-36; claim 42).
It is furthermore not shown in the present application that the FGL peptides of the present application have an improved effect over the individual monomers, which exert according to example 10 of the present application a "significant stimulation of neurite outgrowth of rat hippocampal neurons in vitro" like the FGL peptide.

The skilled person would regard it as an obvious solution to use the linkers of D3 to connect the sequences of D1 or D2 to obtain the fusion proteins of the present application to prevent or treat diseases that are associated with an FGFR.

Hence, the subject-matter of claim 1 lacks an inventive step in the sense of Article 33(3) PCT.

The same reasoning applies, mutatis mutandis, to the subject-matter of the corresponding independent claims 20-25,27-32 and 34 which therefore are also considered not inventive.

Dependent claims 2-19,26 and 33 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of inventive step, see documents D1 to D3 and the corresponding passages cited in the search report.

Industrial applicability

For the assessment of the present claim 34 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claim. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VI
Certain documents cited

Certain published document:

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (SEPARATE SHEET)

International application No.

PCT/DK2004/000527

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim) (day/month/year)*
WO 2004/056865	08.07.2004	18.12.2003	20.12.2002 03.03.2003

Claims

1. A compound comprising two individual peptide sequences, wherein at least one of the two individual peptide sequences comprises an amino acid sequence of the formula

L1-A-L2-B-L3-C-L4-D-L5

wherein

one of A, B, C, D is selected from a hydrophobic amino acid residue,

one of A, B, C, D is selected from a basic amino acid residue, Asn or Gln,

one of A, B, C, D is selected from an acidic amino acid residue, Asn or Gln,

one of A, B, C, D is Gly or Ala, and

L1, L2, L3, L4 and L5 is selected from a chemical bond or an amino acid sequence having n amino acid residues, wherein n is an integer of from 0 to 5, wherein

said peptide sequences are connected to each other through a linker of the formula

X[(A)nCOOH][(B)mCOOH]

n and m independently are an integer of from 1 to 20,

X is HN, $H_2N(CR_2)pCR$, $RHN(CR_2)pCR$, $HO(CR_2)pCR$, $HS(CR_2)pCR$, halogen-$(CR_2)pCR$, $HOOC(CR_2)pCR$, $ROOC(CR_2)pCR$, $HCO(CR_2)pCR$, $RCO(CR_2)pCR$, $[HOOC(A)n][HOOC(B)m]CR(CR_2)pCR$, $H_2N(CR_2)p$, $RHN(CR_2)p$, $HO(CR_2)p$, $HS(CR_2)p$, halogen-$(CR_2)p$, $HOOC(CR_2)p$, $ROOC(CR_2)p$, $HCO(CR_2)p$, $RCO(CR_2)p$, or $[HOOC(A)n][HOOC(B)m](CR_2)p$, wherein p is 0 or integer of from 1 to 20,

A and B independently are a substituted or unsubstituted C_{1-10} alkyl, a substituted or unsubstituted C_{2-10} alkenyl, a substituted or unsubstituted cyclic moiety, a substituted or unsubstituted heterocyclic moiety, a substituted or unsubstituted aromatic moiety, or A and B together form a substituted or unsubstituted cyclic moiety, substituted or unsubstituted heterocyclic moiety, or substituted or unsubstituted aromatic moiety.

2. The compound according to claim 1, wherein the at least one of the two peptide sequences is capable of binding to a functional cell surface receptor.

3. The compound according to claim 2, wherein the functional cell surface receptor is a receptor selected from the family of fibroblast growth factor receptors (FGFRs) comprising FGFR1, FGFR2, FGFR3 and FGFR4.

4. The compound according to claim 2, wherein the at least one of the two peptide sequences is derived from the sequence of a polypeptide selected from the group comprising cell adhesion molecules, cell-surface receptors, heparan sulphate proteoglycans, and metalloproteases, extracellular matrix molecules or growth factors.

5. The compound according to the claim 4, wherein the cell adhesion molecule is selected from the group comprising
- Neural Cell Adhesion Molecule (NCAM) (Swiss-Prot Ass. Nos: P13591, P13595-01, P13595),
- Neural cell adhesion molecule L1 (Swiss-Prot Ass. Nos: Q9QYQ7, Q9QY38, P11627, Q05695, P32004),
- Neural Cell Adhesion Molecule-2 (NCAM-2) (Swiss-Prot Ass. No: P36335)
- Neuron-glia Cell Adhesion Molecule (Ng-CAM) (Swiss-Prot Ass. No: Q03696; Q90933),
- Neural cell adhesion molecule CALL (Swiss-Prot Ass. No: O00533),
- Neuroglian (Swiss-Prot Ass. No: P91767, P20241),
- Nr-CAM (HBRAVO, NRCAM, NR-CAM 12) (Swiss-Prot Ass. Nos: Q92823, O15179, Q9QVN3
- Axonin-1/TAG-1 (Swiss-Prot Ass. Nos: Q02246, P22063, P28685),
- Axonal-associated Cell Adhesion Molecule (AxCAM) (NCBI Ass. No: NP_031544.1; Swiss-Prot Ass. No: Q8TC35),
- Myelin-Associated Glycoprotein (MAG) (Swiss-Prot Ass. No: P20917),
- Neural cell adhesion molecule BIG-1 (Swiss-Prot Ass. No: Q62682),
- Neural cell adhesion molecule BIG-2 (Swiss-Prot Ass. No: Q62845),
- Fasciclin (FAS-2) (Swiss-Prot Ass. No: P22648),
- Neural cell adhesion molecule HNB-3/NB-3 (Swiss-Prot Ass. Nos: Q9UQ52, P97528, Q9JMB8)
- Neural cell adhesion molecule HNB-2/NB-2 (Swiss-Prot Ass. Nos: O94779, P07409, P97527),

- Cadherin (Swiss-Prot Ass. No: Q9VW71),
- Junctional Adhesion Molecule-1 (JAM-1) (Swiss-Prot Ass. Nos: Q9JKD5, O88792),
- Neural cell adhesion F3/F11(Contactin) (Swiss-Prot Ass. Nos: Q63198, P1260, Q12860, Q28106, P14781, O93250),
- Neurofascin (Swiss-Prot Ass. Nos: Q90924, Q91Z60; O42414),
- B-lymphocyte cell adhesion molecule CD22 (Swiss-Prot Ass. Nos: Q9R094, P20273),
- Neogenin (NEO1) (Swiss-Prot Ass. Nos: Q92859, P97603, Q90610, P97798),
- Intercellular Cell Adhesion Molecule-5 (ICAM-5/telencephalin) (Swiss-Prot Ass. Nos: Q8TAM9, Q60625) or
- Galactose binding lectin-12 (galectin-12) (Swiss-Prot Ass. Nos: Q91VD1, Q9JKX2, Q9NZ03) and
- Galactose binding lectin-4 (galectin-4) (Swiss-Prot Ass. No: Q8K419; P38552).

6. The compound according to the claim 4, wherein the cell-surface receptor is selected from the group comprising
- Fibroblast Growth Factor Receptor 1 (FGFR1) (Swiss-Prot Ass. Nos: Q9QZM7, Q99AVV7, Q9UD50, Q63827),
- Fibroblast Growth Factor Receptor 2 (FGFR2) (Swiss-Prot Ass. Nos: Q96KM2, P21802, Q63241),
- Fibroblast Growth Factor Receptor 3 (FGFR3) (Swiss-Prot Ass. Nos: Q95M13, AF487554, Q99052),
- Fibroblast Growth Factor Receptor 4 (FGFR4) (Swiss-Prot Ass. No: Q91742),
- Neurotrophin Tyrosin Kinase Type-2 (NTRKT-2) (Swiss-Prot Ass. No: Q8WXJ5),
- Leukocyte Antigen Related Protein-Tyrosine Phosphatase (LAR-PTPRF) (Swiss-Prot Ass. Nos: Q9EQ17, Q64605, Q64604, Q9QW67, Q9VIS8 P10586),
- Nephrin (Swiss-Prot Ass. Nos: Q925S5, Q9JIX2, Q9ET59, Q9R044, Q9QZS7, Q06500),
- Protein-Tyrosine Phosphatase Receptor type S (PTPRS) (Swiss-Prot Ass. Nos: Q64699, Q13332, O75870),
- Protein-Tyrosine Phosphatase Receptor type kappa (R-PTP-kappa) (Swiss-Prot Ass. No: Q15262),

- Protein-Tyrosine Phosphatase Receptor type D (PTPRD) (Swiss-Prot Ass. Nos: Q8WX65, Q9IAJ1, P23468, Q64487),
- Ephrin type-A receptor 8 (EPHA8/Tyrosine-Protein Kinase Receptor EEK) (Swiss-Prot Ass. Nos: O09127, P29322),
- Ephrin type-A receptor 3 (EPHA8/Tyrosine-Protein Kinase Receptor ETK-1/CEK4) (Swiss-Prot Ass. No: P29318),
- Ephrin type-A receptor 2 (Swiss-Prot Ass. No: Q8N3Z2)
- Insulin Receptor (IR) (Swiss-Prot Ass. No: Q9PWN6)
- Insulin-like Growth Factor-1 Receptor (IGF-1) (Swiss-Prot Ass. Nos: Q9QVW4, P08069, P24062, Q60751, P15127, P15208)
- Insulin-related Receptor (IRR) (Swiss-Prot Ass. No: P14616),
-Tyrosine-Protein Kinase Receptor Tie-1 (Swiss-Prot Ass. Nos: 06805, P35590, Q06806),
- Roundabout receptor-1 (robo-1) (Swiss-Prot Ass. Nos: O44924, AF041082, Q9Y6N7),
- Neuronal nicotinic acetylcholine receptor alpha 3 subunit (CHRNA3) (Swiss-Prot Ass. Nos: Q8VHH6, P04757, Q8R4G9, P32297)
- Neuronal acetylcholine receptor alpha 6 subunit (Swiss-Prot Ass. Nos: Q15825, Q9R0W9)
- Platelet-Derived Growth Factor Receptor Beta (PDGFRB) (Swiss-Prot Ass. Nos: Q8R406, Q05030),
- Interleukin-6 Receptor (IL-6R) (Swiss-Prot Ass. No: Q00560),
- Interleukin-23 Receptor (IL-23R) (Swiss-Prot Ass. No: AF461422),
- Beta-common cytokine receptor of IL-3, IL5 and GmCsf (Swiss-Prot Ass. No: P32927)
- Cytokine Receptor-Like molecule 3 (CRLF1) (Swiss-Prot Ass. No: Q9JM58),
- Class I Cytokine Receptor (ZCYTOR5) (Swiss-Prot Ass. No: Q9UHH5)
- Netrin-1 receptor DCC (Swiss-Prot Ass. No: P43146),
- Leukocyte Fc Receptor-like Protein (IFGP2) (Swiss-Prot Ass. Nos: Q96PJ6, Q96KM2),
- Macrophage Scavenger Receptor 2 (MSR2) (Swiss-Prot Ass. No: Q91YK7) and
- Granulocyte Colony Stimulating Factor Receptor (G-CSF-R) (Swiss-Prot Ass. No: Q99062).

7. The compound according to the claim 4, wherein the heparan sulphate proteoglycan is perlecan (Swiss-Prot Ass. No: P98160).

8. The compound according to the claim 4, wherein the metalloprotease is selected from the group comprising
- ADAM-8 (Swiss-Prot Ass. No: Q05910),
- ADAM-19 (Swiss-Prot Ass. Nos: Q9H013, O35674),
- ADAM-8 (Swiss-Prot Ass. No: P78325),
- ADAM-12 (Swiss-Prot Ass. Nos: O43184, Q61824),
- ADAM-28 (Swiss-Prot Ass. Nos: Q9JLN6, Q61824, Q9XSL6, Q9UKQ2),
- ADAM-33 precursor (Swiss-Prot Ass. Nos: Q8R533, Q923W9),
- ADAM-9 (Swiss-Prot Ass. Nos: Q13433, Q61072),
- ADAM-7 (Swiss-Prot Ass. NoS: Q9H2U9, O35227, Q63180),
- ADAM-1A Fertilin alpha (Swiss-Prot Ass. No: Q8R533),
- ADAM-15 (Swiss-Prot Ass. Nos: Q9QYV0, O88839, Q13444),
- Metalloproteinase-desintegrin domain containing protein (TECAM) (Swiss-Prot Ass. No: AF163291), and
- Metalloproteinase 1 (Swiss-Prot Ass. Nos: O95204, Q9BSI6).

9. The compound according to the claim 4, wherein the extracellular matrix molecule is selected from the group comprising
- Collagen type VII (Swiss-Prot Ass. No: Q63870),
- Fibronectin (Swiss-Prot Ass. Nos: Q95KV4, Q95KV5, P07589, Q28377, U42594, O95609, P11276), or
- Tenascin-R (Swiss-Prot Ass. Nos: Q15568, O00531, Q90995, P10039).

10. The compound according to the claim 4, wherein the growth factor is Cytokine-like factor-1 (CLF-1) (Swiss-Prot Ass. No:O75462).

11. The compound according to any of the claims 1 to 10, wherein the at least one of the two peptide sequences is a peptide fragment having the amino acid sequence selected from
EVYVVAENQQGKSKA (SEQ ID NO 1),
NIEVWVEAENALGKKV (SEQ ID NO: 2),
ATNRQGKVKAFAHL (SEQ ID NO: 3),

RYVELYVVADSQEFQK (SEQ ID NO: 4)
VAENSRGKNVAKG (SEQ ID NO: 5),
GEYWCVAENQYGQR (SEQ ID NO: 6),
RLAALNGKGLGEIS (SEQ ID NO: 7),
KYIAENMKAQNVAKEI (SEQ ID NO: 8),
TIMGLKPETRYAVR (SEQ ID NO: 9),
KGLGEISAATEFKT (SEQ ID NO: 10),
NMGIWVQAENALG (SEQ ID NO: 11),
IWVQAENMLG (SEQ ID NO: 12),
EIWVEATNRLG (SEQ ID NO: 13),
VWVQAANALG (SEQ ID NO: 14),
EVWIEKDPAKGRI (SEQ ID NO: 15),
ATNKGGEVKKNGHL (SEQ ID NO: 16),
KYVELYLVADYLEFQK (SEQ ID NO: 17),
RYVELYVVVDNAEFQ (SEQ ID NO: 18),
KYVELVIVADNREFQR (SEQ ID NO: 19),
KYIEYYLVLDNGEFKR (SEQ ID NO: 20),
RYLELYIVADHTLF (SEQ ID NO: 21),
KYVEMFVVVNHQRFQ (SEQ ID NO: 22) ,
RYVELFIVVDKERY (SEQ ID NO: 23),
KYVELFIVADDTVYRR (SEQ ID NO: 24),
KFIELFVVADEYVYRR (SEQ ID NO: 25),
KIVEKVIVADNSEVRK (SEQ ID NO: 26),
VELVIVADHSEAQK (SEQ ID NO: 27),
VAENSRGKNIAKG (SEQ ID NO: 28),
IAENSRGKNVARG (SEQ ID NO: 29),
AENSRGKNSFRG (SEQ ID NO: 30),
IASNLRGRNLAKG (SEQ ID NO: 31),
IPENSLGKTYAKG (SEQ ID NO: 32),
IAENMKAQNEAK (SEQ ID NO: 33),
QFIAENMKSHNETKEV (SEQ ID NO: 34),
GEYWCVAKNRVGQ (SEQ ID NO: 35),
GSYTCVAENMVGK (SEQ ID NO: 36),
GKYVCVGTNMVGER (SEQ ID NO: 37),
GNYTCVVENEYG (SEQ ID NO: 38),

GEYTCLAGNSIG (SEQ ID NO: 39),
QYYCVAENGYG (SEQ ID NO: 40),
GEYYQEAEQNGYG (SEQ ID NO: 41),
GNYTCLVENEYG (SEQ ID NO: 42),
GMYQCLAENAYG (SEQ ID NO: 43),
GMYQCAENTHG (SEQ ID NO: 44),
GIYYCLASNNYG (SEQ ID NO: 45),
GGYYCTADNSYG (SEQ ID NO: 46),
GEYQCFARNDYG (SEQ ID NO: 47),
GEYFCLASNKMG (SEQ ID NO: 48),
GEYQCFARNKFG (SEQ ID NO: 49),
GEYFCLASNKMG (SEQ ID NO: 50),
GGYYCTADNNYG (SEQ ID NO: 51),
GNYSCEAENAWGTK (SEQ ID NO: 52),
GEYTCLAENSLG (SEQ ID NO: 53),
GEYECVAENGRLG (SEQ ID NO: 54),
GNYTCVVENKFGR (SEQ ID NO: 55),
GEYTCLAGNSIG (SEQ ID NO: 56),
GEYFCVASNPIG (SEQ ID NO: 57),
EYTCIANNQAGE (SEQ ID NO: 58),
GMYQCVAENKHLG (SEQ ID NO: 59),
GEYMCTASNTIGQ (SEQ ID NO: 60),
EYVCIAENKAGEQ (SEQ ID NO: 61),
GDYTLIAKNEYGK (SEQ ID NO: 62),
GFYQCVAENEAG (SEQ ID NO: 63),
GKYECVATNSAGTR (SEQ ID NO: 64),
GEYFCVYNNSLG (SEQ ID NO: 65),
GEYECAATNAHGR (SEQ ID NO: 66),
GAYWCQGTNSVGK (SEQ ID NO: 67),
GTYSCVAENILG (SEQ ID NO: 68),
RVAAVNGKGQGDYS (SEQ ID NO: 69),
RVAAINGCGIGPFS (SEQ ID NO: 70),
AVLNGKGLG (SEQ ID NO: 71),
ALNGQGLGATS (SEQ ID NO: 72),
RLAAKNRAGLGE (SEQ ID NO: 73),

RLGVVTGKDLGEI (SEQ ID NO: 74),
TVTGLKPETSYMVK (SEQ ID NO: 75),
TLTGLKPSTRYRI (SEQ ID NO: 76),
TLTGLQPSTRYRV (SEQ ID NO: 77),
TLLGLKPDTTYDIK (SEQ ID NO: 78),
TLQGLRPETAYELR (SEQ ID NO: 79),
TLRGLRPETAYELR (SEQ ID NO: 80),
TLMNLRPKTGYSVR (SEQ ID NO: 81),
TVSGLKPGTRY (SEQ ID NO: 82),
TISGLKPDTTY (SEQ ID NO: 83),
TLQGLKPDTAY (SEQ ID NO: 84),
LRGLKPWTQYAV (SEQ ID NO: 85),
IDGLEPDTEYIVR (SEQ ID NO: 86),
LQGLKPWTQYAI (SEQ ID NO: 87),
TITGLEPGTEYTIQ (SEQ ID NO: 88),
GLKPWTQYAV (SEQ ID NO: 89),
TLASLKPWTQYAV (SEQ ID NO: 90),
LMGLQPATEYIV (SEQ ID NO: 91),
KGMGPMSEAVQFRT (SEQ ID NO: 92),
TLTGLKPDTTYDVK (SEQ ID NO: 93),
ISGLQPETSYSL (SEQ ID NO: 94),
TLLGLKPDTTYDIK (SEQ ID NO: 95),
TISGLTPETTYSI (SEQ ID NO: 96),
GNYSCLAENRLGR (SEQ ID NO: 97),
GNYTCVVENRVG (SEQ ID NO: 98),
GTYHCVATNAHG (SEQ ID NO: 99),
LSHNGVLTGYLLSY (SEQ ID NO: 100),
NGVLTGYVLRY (SEQ ID NO: 101),
NGVLTGYNLRY (SEQ ID NO: 102),
NGNLTGYLLQY (SEQ ID NO: 103),
VDENGVLTGYKIYY (SEQ ID NO: 104),
THNGALVGYSVRY (SEQ ID NO: 105),
NGILTEYILKY (SEQ ID NO: 106),
NGILIGYTLRY (SEQ ID NO: 107),
THSGQITGYKIRY (SEQ ID NO: 108),

NGKITGYIIYY (SEQ ID NO: 109),
LSHNGIFTLY (SEQ ID NO: 110),
NGILTEYTLKY (SEQ ID NO: 111),
LDPNGIITQYEISY (SEQ ID NO: 112),
NGKITGYIIYY (SEQ ID NO: 113),
HLEVQAFNGRGSGPA (SEQ ID NO: 114),
HLTVRAYNGAGYGP (SEQ ID NO: 115),
HLSVKAYNSAGTGPS (SEQ ID NO: 116),
HLAVKAYNSAGTGPS (SEQ ID NO: 117),
NLEVRAFNSAGDGP (SEQ ID NO: 118),
HLTVLAYNSKGAGP (SEQ ID NO: 119),
LRVLVFNGRGDGP (SEQ ID NO: 120),
HIDVSAFNSAGYGP (SEQ ID NO: 121),
HLAVELFNGR (SEQ ID NO: 122),
LELQSINFLGGQPA (SEQ ID NO: 123),
HFTVRAYNGAGYGP (SEQ ID NO: 124),
HLEVQAFNGRGSQPA (SEQ ID NO: 125),
VIADQPTFVKYLIK (SEQ ID NO: 126),
TIKGLRPGVVYEGQ (SEQ ID NO: 127),
TLTELSPSTQYTVK (SEQ ID NO: 128),
TLDDLAPDTTYLVQ (SEQ ID NO: 129),
TVSDVTPHAIYTVR (SEQ ID NO: 130),
IIRGLNASTRYLFR (SEQ ID NO:131),
TLMNLRPKTGYSVR (SEQ ID NO:132),
TLTGLKPGTEYEVR (SEQ ID NO: 133),
GPEHLMPSSTYVAR (SEQ ID NO: 134),
RVTGLTPKKTYEFR (SEQ ID NO: 135),
LTGLKPGTEYEFR (SEQ ID NO: 136),
EVRVQAVNGGGNGPP (SEQ ID NO: 137),
LIKVVAINDRGE (SEQ ID NO: 138),
VVSIIAVNGREE (SEQ ID NO: 139),
VVSVYAQNQNGE (SEQ ID NO: 140),
TISLVAEKGRHK (SEQ ID NO: 141),
HLEVQAFNGRGSGPA (SEQ ID NO: 142),
HVEVQAFNGRGLGPA (SEQ ID NO: 143),

HVEVQAFNGRGLGPA (SEQ ID NO: 144),
EFRVRAVNGAGEG (SEQ ID NO: 145), or
VARVRTRLAPGSRLS (SEQ ID NO: 146), or
or a fragment, or a variant, or homologue thereof,
wherein
said fragment is an amino acid sequence which has at least 40% of the length of a sequence selected from SEQ ID NOs:1-146 and which is capable of binding to fibroblast growth factor receptor,
said variant is an amino acid sequence which has at least 60% of homology to a sequence selected from SEQ ID NOs: 1-146 and which is capable of binding to fibroblast growth factor receptor, and
said homologue is an amino acid sequence which has at least 20% homology to a sequence selected from SEQ ID NOs: 1-146 and which is capable of binding to fibroblast growth factor receptor.

12. The compound according to claims 1 to 10, wherein the at least one of the two peptide sequences is SEQ ID NO: 1 (EVYVVAENQQGKSKA), or a fragment, variant, or homologue of said sequence.

13. The compound of claim 12, wherein the variant or homologue of SEQ ID NO: 1 is selected from SEQ ID NOs: 2-9, 100 or 125,

14. The compound according to claims 1 to 10, wherein the at least one of the two peptide sequences is SEQ ID NO: 2 (NIEVWVEAENALGKKV), or a fragment, variant or homologue of said sequence.

15. The compound according to any of the preceding claims, wherein the compound comprises two individual peptide fragments comprising different amino acid sequences, said different amino acid sequences being selected from any of the peptide fragments of claim 11.

16. The compound according to any of the preceding claims, wherein the compound comprises two peptide fragments comprising the identical amino acid sequence, said amino acid sequence being selected from any of the peptide fragments of claim 11.

17. The compound according to claim 16, wherein the peptide fragments are independently having the sequence EVYVVAENQQGKSKA (SEQ ID NO: 1).

18. The compound according to claim 16, wherein the peptide fragments are independently having the sequence NIEVWVEAENALGKKV (SEQ ID NO: 2).

19. The compound according to claim 15, wherein one of the two peptide fragments is having the sequence EVYVVAENQQGKSKA (SEQ ID NO: 1), and the other is having the sequence NIEVWVEAENALGKKV (SEQ ID NO: 2).

20. The compound according to any of the preceding claims, said compound being obtained by a method for preparing an LPA enabling presentation of sequence(s) as defined in claim 11 comprising the steps of
(a) providing by solid phase synthesis or fragment coupling ligands comprising desired sequence(s), the ligands being attached to a solid phase,
(b) if nessesary, deprotecting any N-terminal amino acid groups while th eligands/s) are still attached to the solid phase,
(c) reacting the ligand(s) having unprotected N-terminal groups with an achiral di- tri- or tetracarboxylic acid so as to provide a construct having a ring structure, and
(d) cleaving the construct from the solid phase so as to provide an LPA comprising ligands having free C-terminal groups.

21. A pharmaceutical composition comprising a compound as defined in claims 1-20.

22. Use a compound as defined in any of the claims 1-20 for the manufacture of a medicament for treatment of conditions of the central and peripheral nervous system associated with postoperative nerve damage, traumatic nerve damage, impaired myelination of nerve fibers, postischaemic damage, e.g. resulting from a stroke, Parkinson's disease, Alzheimer's disease, Huntington's disease, dementias such as multiinfarct dementia, sclerosis, nerve degeneration associated with diabetes mellitus, disorders affecting the circadian clock or neuro-muscular transmission, and schizophrenia, mood disorders, such as manic depression; for

treatment of diseases or conditions of the muscles including conditions with impaired function of neuro-muscular connections, such as after organ transplantation, or such as genetic or traumatic atrophic muscle disorders; or for treatment of diseases or conditions of various organs, such as degenerative conditions of the gonads, of the pancreas such as diabetes mellitus type I and II, of the kidney such as nephrosis and of the heart, liver and bowel.

23. Use a compound as defined in any of the claims 1-20 for the manufacture of a medicament for the treatment of postoperative nerve damage, traumatic nerve damage, impaired myelination of nerve fibers, postischaemic, e.g. resulting from a stroke, Parkinson's disease, Alzheimer's disease, Huntington's disease, dementias such as multiinfarct dementia, sclerosis, nerve degeneration associated with diabetes mellitus, disorders affecting the circadian clock or neuro-muscular transmission, and schizophrenia, mood disorders, such as manic depression.

24. Use a compound as defined in any of the claims 1-20 for the manufacture of a medicament for the promotion of wound-healing.

25. Use a compound as defined in claims 1-20 for the manufacture of a medicament for the treatment of cancer

26. The use according to claim 25, wherein the cancer is any type of solid tumors requiring neoangiogenesis

27. Use a compound as defined in any of the claims 1-20 for the manufacture of a medicament for the prevention of death of heart muscle cells, such as after acute myocardial infarction, or after angiogenesis

28. Use a compound as defined in any of claims 1-20 for the manufacture of a medicament for revascularsation.

29. Use a compound as defined in any of the claims 1-20 for the manufacture of a medicament for the stimulation of the ability to learn and/or the short and/or long-term memory

30. Use a compound as defined in any of the claims 1-20 for the manufacture of a medicament for the prevention of cell death due to ischemia.

31. Use a compound as defined in any of the claims 1-20 for the manufacture of a medicament for the prevention of body damages due to alcohol consumption.

32. Use a compound as defined in any of the claims 1-20 for the manufacture of a medicament for the treatment of prion diseases.

33. Use of a medicament of any of the claims 22-31 or pharmaceutical composition according to claim 21 for the treatment of a disease or condition as defined in claims 22-31.

34. A method of treatment of an individual in need comprising a step of administering to said individual a compound as defined in any of the claims 1 to 20, and/or a pharmaceutical composition as defined in claim 21, and/or medicament as defined in claims 22-31.